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Comparative Studies on Hypotensive Mechanism of Three Different Alpha 2—Adrenoceptor Agonists

Kenichi Kujime[1], Michiyo Su[2], Hisayuki Sawatari[3] and Yasuyuki Ueba[1]

Alpha2—adrenoceptor agonists exert hypotensive effects by acting mainly via receptors located in the central nervous system. Although there are several reports available on the different actions among these drugs, the comparative studies of the hypotensive mechanism have not been extensively performed yet. In rabbits anesthetized with urethane, arterial pressure (AP) and renal sympathetic nerve activity (RNA) were recorded simultaneously. On the basis of the identical pharmacological action, Guanfacine (Gf) and Guanabenz (Gb) were administered intravenously in cumulative dose of 10, 30, 100, 300 μg/kg and Clonidine (Cl) was also given 1, 3, 10, 30 μg/kg, respectively. Although the magnitudes were different, each drug initially elevated AP which was followed by hypotensive phase, while RNA markedly decreased at the initial hypertensive phase and returned to the control level gradually. The initial increase in AP, representing the stimulating action on alpha receptor on the arterial wall, was 7% in Cl, 3% in Gb and 14% in Gf.

When bilateral baroceptors were denervated for the investigation of the central action, depression of RNA by Cl (−23%) was much greater than in the case of Gb (−11%) and Gf (−6%).

Thus, these drugs have an agonistic action on alpha2—receptor. However, as for the action on sympathetic nervous system, Cl has more dominant suppressive action on the central nervous system, while Gf more strongly stimulates the peripheral presynaptic alpha2—receptor. Although Gb has an action of two other drugs, it is speculated to have more activating action on baroreflex.

Key Words

Alpha2—adrenoceptor agonists,
Renal sympathetic nerve activity,
Rabbit,
Peripheral action,
Central action.

INTRODUCTION

Recently, several kinds of alpha2—adrenoceptor agonist are available for the treatment of hypertension (1). Although there are some reports on the different actions of these drugs, it is not clear yet how these drugs exert effects on sympathetic nerve activity and hemodynamics quantitatively.

The antihypertensive effect of the drugs is mediated, at least in a part, by a way of the central nervous system where it acts as an alpha—adrenoceptor agonist. This, in turn, leads to reduced sympathetic nervous activity and decreased blood pressure (2). Therefore the drug is classified as centrally acting antihypertensive one.

On the other hand, peripheral factors at the level of the sympathetic terminal

School of Allied Medical Sciences, Kobe University[1], Department of Internal Medicine, Division 1, Kobe University School of Medicine[2] Kobe Takasago Municipal Hospital[3], Gakasago, Japan.

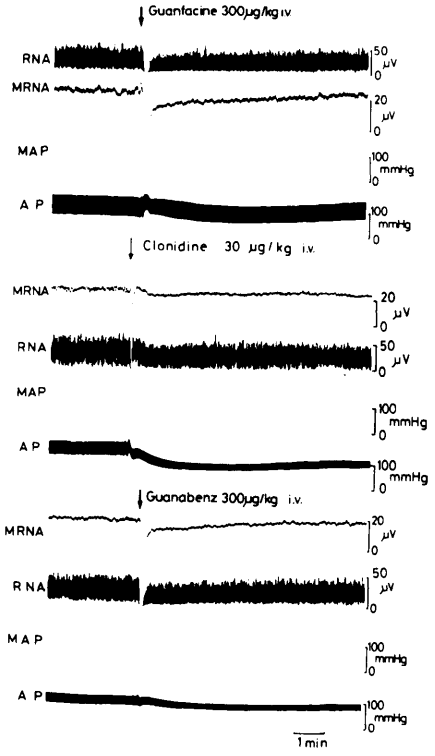


Figure 1. Typical changes of RNA and AP induced by each drug. Immediately after the administration at arrow, arterial pressure was elevated and followed by hypotension. In contrast, renal nerve activity showed marked decrease which was followed by gradual recovery. Note the grade of the changes was different by each drug. The following abbreviations were used. AP: arterial pressure. RNA (renal sympathetic nerve activity) M: mean

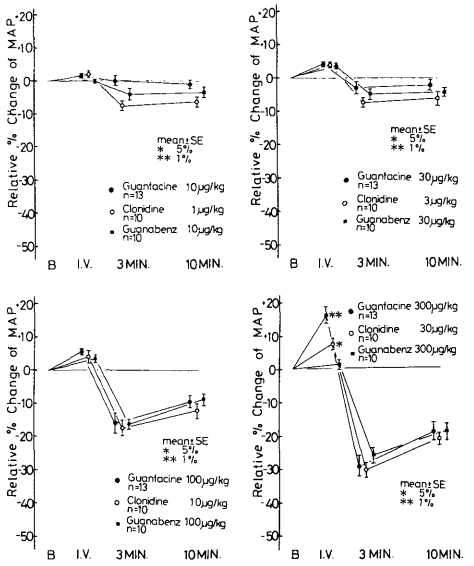


Figure 2. Changes in AP
The figure shows the changes in AP in baroceptor-intact rabbits. The numbers of animals were 13 in Gf, 10 in Cl and 10 in Gb.

varicosity may have either a presynaptic or postsynaptic action. The amount of norepinephrine released by nerve impulses may be controlled by presynaptic receptors (3). The stimulation of presynaptic receptor regulates the norepinephrine release from the sympathetic nerve terminal. These mechanisms may control the hypotensive effects to some extent.

The aim of our study is to compare the peripheral and central effects of three alpha2—adrenoceptor agonists i.e., Clonidine (Cl), Guanfacine (Gf) and Guanabenz (Gb) with regard to hypotensive mechanism. As a comparative study, the effects of the drugs on arterial pressure (AP), renal sympathetic nerve activity (RNA) and plasma norepinephrine (NE) were examined in anesthetized rabbits.

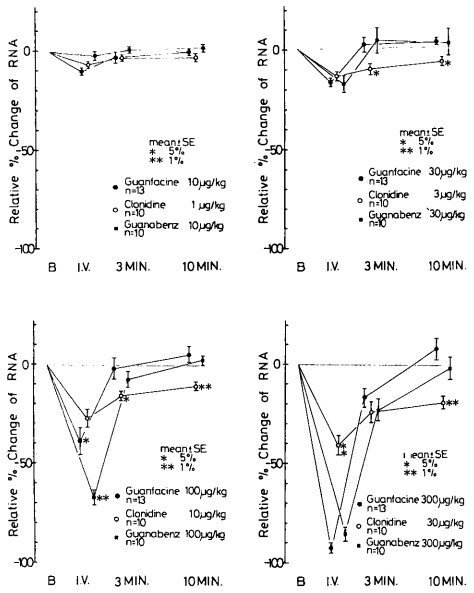


Figure 3. Changes in AP after denervation
The figure shows the changes in AP in baroceptor-denervated rabbits. The numbers of animals were 9 in Gf, 8 in Cl and 5 in Gb.

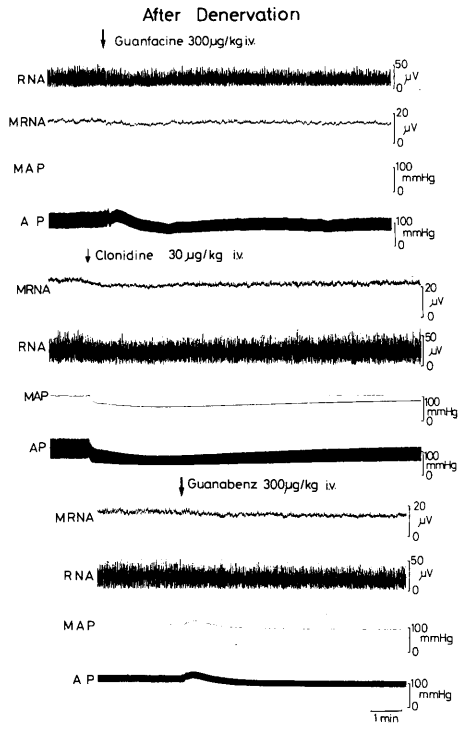


Figure 4. Typical changes of RNA and AP obtained in rabbits with sinoaortic denervation.
Immediately after the administration at arrow, arterial pressure (AP) was elesated and was followed by hypotension. However, initial decrease in RNA was disappeared.

METHODS AND MATERIALS

(1) Surgical Procedure

Fifty-five adult rabbits, weighing from 2.5 to 3.0 kg, were anesthetized with urethane (1200mg/kg) administered intraperitoneally. After a tracheotomy was performed, each rabbit was ventilated on mixture of oxygen and room air using a Harvard type respirator pump.

The right femoral vein was cannulated for intravenous administration of drugs. Arterial pressure was recorded through a cannula inserted into left femoral artery. The rectal temperature was also monitored and maintained at 38°C with a heat pad.

Efferent sympathetic nerve activity was recorded from a branch of the left renal nerve. The nerve was exposed under a binocular microscope and placed on silver-silver bipolar electrode. The nerve activity was recorded using a high gain amplifier and measured in arbitrary unit of integrated amplitude.

(2) Protocol for Intervention

After all paramenters were stabilized and the control level was obtained,

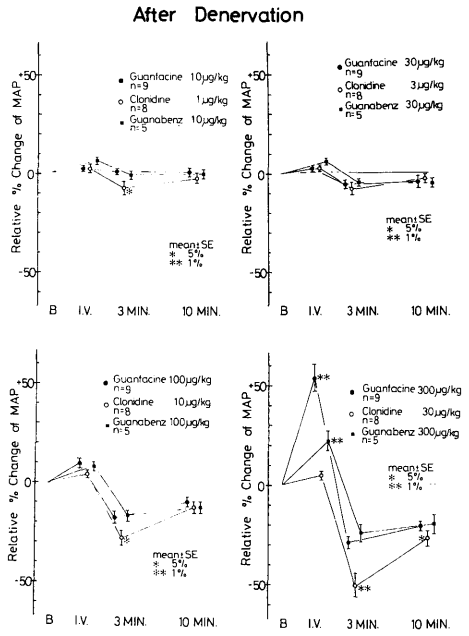


Figure 5. Changes in AP after denervation
The figure shows the changes in AP in baroceptor-denervated rabbits. The numbers of animals were 13 in Gf, 10 in Cl and 10 in Gb.

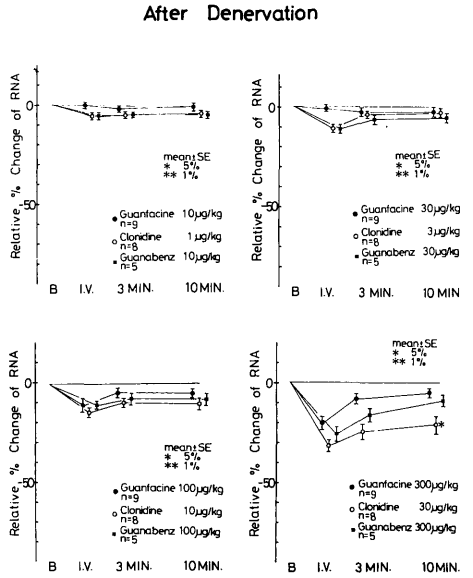


Figure 6. Changes in RNA after denervation
The statistical results obtained in baroreceptor-denervated rabbits. The numbers of animals were the same as in Fig. 5.

abbits were divided into following three groups.

1. Effects of drugs on renal sympathetic nerve activity and hemodynamics

On the basis of the identical pharmacological action, Guanfacine (Gf) and Guanabenz (Gb) were administered intravenously in cumulative dose of 10, 30, 100, 300 μg/kg and Clonidine (Cl) was also given 1, 3, 10, 30 μg/kg, respectively in 33 rabbits. The effects of the drugs were observed for 10 minutes. The followed administration was repeated at an interval of 30 minutes. The statistical analysis of the present report was only performed with values obtained in each maximum dose.

The values of parameters were measured at 3 points after the administration, i.e., at the points of immediately, 3 minutes and 10 minutes. The relative % change was calculated in the comparison with the control value which was obtained just before the administration.

2. Denervation of bilateral sinoaortic nerve

For the purpose of the removal of afferent inputs to the central nervous system, bilateral carotid sinus nerve and vagoaortic nerve were denervated in 22 rabbits. Because of diminished modifica-

tion from peripheral inputs, the changes in RNA mainly show the central action. The results were compared with the non-denervated group by each drug.

(3) Data Analysis

For the data analysis, mean values of AP and RNA were employed. The results are expressed as mean ± S.E.M. in figures. Statistical analysis was performed with Student's t test or ANOVA test (5). Significance was accepted at the $P < 0.05$.

(4) Materials

The drugs used in this experiment were as in the following.: Guanfacine (Sandoz), Guanabenz (Wyeth), Clonidine (Boehringer), Gallamine (Teikoku Sangyo Co), Urethane (Wako Chem. Co.).

RESULTS

(1) Effects of drugs on renal sympathetic nerve activity and hemodynamics

As shown in figure 1, AP was increased immediately after the administration of each drug. RNA showed remarkable concomitant suppression. This response indicated that the initial suppression in RNA might be developed by baroreflex. After this phase, AP changed into hypotension which was followed by gradual elevation in association with RNA.

Figure 2 and 3 summarizes the results of AP and RNA. Although the magnitude was different by each drug, RNA was markedly depressed (61% in Cl, 18% in Gb, 7% in Gf) as a result of concomitant initial increase in AP (107% in Cl, 10% in Gb, 114% in Gf).

This initial hypertension was followed by hypotension. Three minutes after the administration, RNA and AP were decreased. After 10 minutes RNA was still below the control level in Cl (78%). In contrast, RNA returned to the control level in Gb (98%) and overshot the level in Gf (109%) in spite of the decrease in AP (77% in Cl, 80% in Gb, 80% in Gf). Because the hypotensive responses of the drugs at 10 minutes did not show statistical difference, it was indicated that the pharmacological hypotensive effects were approximately the same other.

(2) Response in denervated animals

In figure 4, it is shown the typical response obtained in a rabbit with bilateral sinoaortic denervation. After the denervation was completed, the drugs were administered intravenously. Figure 5 and 6 show the results of AP and RNA in the same manner as Figure 2 and 3. There was smaller initial decrease in RNA in contrast to greater increase in AP. Initial increase in AP was most significant in Gf (151%) and least in Cl (108%). Ten minutes after the administration, RNA in each group was still lower than the control level. The grade of suppression in RNA was the most significant in Cl (77%) and the least in Gf (93%).

DISCUSSION

In the present study, it was indicated that the three drugs were potent hypotensive agent capable of reducing sympathetic nerve activity via central and peripheral pathway. However, the quantitative grade seems to be different.

Alpha2—receptors are located both in the brain and the periphery. In the brain stem they modulate sympathetic outflow (2). Peripheral alpha2—receptors activate both presynaptic receptors and receptors in blood vessel's wall (3). Therefore, the discussion will be made on the central or peripheral effects separately.

(1) Central Effects

There are many reports on the central action of drugs. The agonists like Cl are usually reported to act mainly via

alpha2–receptors located centrally (2). The sedative effect of the drugs may also be indicative of a central nervous action (5). The neurogenic hypothesis is supported by the therapeutic activity of Cl and related alpha2–agonist drugs as well. These reports (6, 7) showed that alpha2–adrenoceptor agonists induced a drug-related fall in plasma norepinephrine levels, which presumably reflects the reduction in central sympathetic activity and, at least in part, underlies the fall in blood pressure. Furthermore, RNA was suppressed in awaked dogs in the use of Cl (8). However, the comparison among the drugs was not clearly shown in terms of the selectivity.

The present results strongly suggested the central effects by the reduction of RNA in the denervated animals. Because main afferent pathway, which transmitted hemodynamic changes, was eliminated, decreases in RNA should show the central suppressive action alone. The grade of suppression was most marked in Cl which was followed by Gb and Gf.

Because the denervation diminished the prominent initial suppression of RNA, the relationship between the initial increase in AP and concomitant decrease in RNA suggested the sensitivity of baroreflex. Thus, the grade of the sensitization was most significant in Gb and least in Cl. This action might exaggerate the hypotensive mechanism to some extent.

(2) Peripheral Effects

There are several published studies (9) on postjunctional alpha2–receptors in human subjects. These indicate that peripheral alpha2–receptors appear to contribute to the overall peripheral vascular resistance in human subjects as in animals. The initial pressor effect was found to be due to vasoconstriction resulting from the stimulation of peripheral alpha–adrenoceptors. Although the pressor responsiveness to intravenous alpha–agonists with a range of receptor selectivity can be used as an index of selectivity, the response should be measured without modulation of baroreflex (10, 11). Therefore, the action was most significant in Gf and least in Cl in denervated animals.

In summary, these drugs have agonistic action on alpha2–receptor. However, as for the action on the sympathetic nervous system, Cl has more dominant suppressive action via the central nervous system, while Gf more strongly stimulates the peripheral presynaptic alpha2–receptor. Gb has intermediate action between the other two drugs.

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